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Evaluation of Acute and Sub-Acute Oral Toxicities of *Momordica foetida* Schumach. (Cucurbitaceae) Leaves Methanol Extract in Wistar Rats

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Abstract

Momordica foetida is a plant widely used in tropical Africa to manage gastroenteric diseases. Previous studies demonstrated interesting antibacterial activity against human pathogenic bacteria. However, the security or toxicity of methanol leaf extract has not been determined yet. The aim of this study was to evaluate the acute and sub-acute toxicity of the leaf extract of *Momordica foetida*. In the acute toxicity study, a single oral dose of 5000 mg/kg body weight was administered to rats which were observed for 14 days in order to identify signs of toxicity or death. In the sub-acute toxicity, the animals were treated with 250, 500 and 1000 mg/kg of the extract for 28 consecutive days. Body weights and behavior were noted throughout the experiment. Upon treatment, blood and urine were collected for hematological and biochemical analysis. Liver, lungs, heart, kidneys, testes and ovaries were analyzed for relative weights and histopathology. The acute toxicity study of *M. foetida* leaf extract revealed no signs of toxicity related to the treatment, indicating that the median-lethal-dose (LD50) value is greater than 5000 mg/Kg of body weight. In the sub-acute toxicity assay, the extract did not affect the general behavior of animals, meanwhile, it led to a significant increase in the levels of red blood cells, platelets, hemoglobin, granulocytes and Mid-Cells (MIDs). Biochemical parameters showed an increase in total cholesterol, HDL cholesterol, serum urea, serum and urinary glucose and a decrease in urinary proteins, serum creatinine, urinary urea levels, serum activities of AST, ALT and proteins levels, as well as increases in lung, spleen and ovaries relative weight were no-

ticed, all compared to control animals. Histological analysis revealed a normal architecture of kidneys, liver, heart, lung, ovaries and testes. This study provides valuable data on the safety of *per os* administration of *Momordica foetida* leaf methanol extract that could be very useful for future assays.

Keywords

Momordica foetida, Acute Toxicity, Sub-Acute Toxicity, Biochemical Parameters, Hematological Parameters

1. Introduction

Plant extracts and derivative products with pharmacological properties have demonstrated their capacity of fighting against infectious diseases [1]. Many studies reported the use of these plants in folkloric medicine to cure many ailments. Some investigations have demonstrated the ability of medicinal plants in preventing and curing many diseases. Plants have always been widely used by human beings as a food source and also for their curative/preventive properties against several diseases [2]. Nowadays, plant materials present undeniable medicinal interest because of numerous natural therapeutic products of plant origin that can be used for facing the continuous increase in resistance towards synthetic antibiotics [3]. The administration of these natural products or synthetic drugs to a biological system may induce different types of interactions and a series of dose-related responses. In most cases, these responses are desired and useful, but there are some additional effects that are not advantageous [4]. Recent studies carried out by Ekor [5] showed that many herbal medicines cause serious toxicity to their users. Moreover, the toxicity associated with the repeated use of synthetic drugs contributes to a greater demand for phytotherapy and natural extracts considered of lesser toxicity. Their safety must be studied thoroughly to maximize their benefits to mankind.

Momordica foetida is a plant species belonging to the Cucurbitaceae family. Traditionally, the leaf and the fruit of the plant are used in Cameroon in fighting yellow fever, malaria, diabetes and diarrhea during childbirth [6]. The plant is also used in diabetes, hypertension, stroke, dysentery, stomachache, ulcers, leprosy and gonorrhea relief [7]. Available pharmacological data revealed that the methanol leaf extract of the plant is significantly protective against the toxicity induced by parastar (insecticide) on the duodenal and pancreatic function of Wistar rats when administrated during sixty-four days [8]. The extract also prevents behavioral impairment, motor incoordination and brain oxidative stress induced by subchronic exposure to parastar pesticide formulation [9]. Methanol extract showed high lethal activity against *Anopheles gambiae* and *Anopheles coluzzii* larvae after 24 h exposure. Meanwhile, the extract did not show any significant change in Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or Alkaline Phosphatase (ALP) during acute toxicity at the doses of

1117.3 mg/kg and 2039.7 mg/kg body weight in female Wistar rats [10]. The petrol ether/ethyl acetate extract of the plant showed significant antiplasmodial activity with Inhibitory Concentration 50 (IC50) values of 7.3 µg/mL (poW) and 13.0 µg/mL (Dd2) against the chloroquine-sensitive poW strain and the multiresistant Dd2 clone of *Plasmodium falciparum* respectively [11].

Previous phytochemical investigations on *M. foetida* led to the isolation of Momordiside A (3β-hydroxy-7-oxo-23(R)-cucurbita-5,24-diene-23-O-β-D-glucopyranoside), Momordiside B (3β-hydroxy-7-β-methoxy-23(R)-cucurbita-5,24-diene-23-O-β-D-glucopyranoside, Momordin (23,24,25,26,27-pentanorcurcubitacin), 6-kaemferol-7-O-β-D-glucopyranoside and β–sitosterol-3-O-β-D-glucoside, β–sitosterol [12]. The best-suited secondary metabolite from this plant is 3β,7β-dihydroxyl-cucurbita-5,23,25-trien-19-al (Triterpenes) which possesses a good antibacterial activity (MIC ranging from 7.8 to 250 µg/mL) against some bacteria [13]. Recent studies carried out by our research team led to findings that methanol extract of *Momordica foetida* showed remarkable antibacterial activity against gastroenteric bacteria (MICs values ranging between 32 and 1024 µg/mL) and improved (2 to 64 times) the activity of Aminosides (GEN, KAN, STR), Cyclins (DOX, TET), Macrolides (ERY), Quinolones (NOR), and β-lactams (AMX) on selected multidrug-resistant bacteria.

Despite these impressive pharmacological potentials of *Momordica foetida*, no scientific study has focused on its potentially harmful effects when administered in single or repeated doses. Hence, the objective of this study was to evaluate the acute and sub-acute oral toxicities of a methanol leaf extract of *Momordica foetida* on Wistar rats.

2. Materials and Methods

2.1. Plant Material

Momordica foetida leaves used in the experiment were collected at Bali Nyonga (Mezam division, North-West region, Cameroon) in April 2018. The identification of the plant was done at the National Herbarium of Cameroon, compared to the reference sample number 8114/SRFK.

2.2. Experimental Animals

Ten female Wistar rats aged between 8 and 12 weeks, weighing 100 - 150 g were used for acute toxicity study while forty Wistar rats (20 males and 20 females) aged between 8 and 12 weeks, weighing 150 - 200 g, were used for sub-acute toxicity study. All these animals were purchased at the Laboratory of Animal Biology, University of Douala and acclimatized for two weeks prior to experiments. They were fed on daily basis with a standard rat diet and tap water *ad libitum* and maintained less than 12 hours day and night cycle conditions. The animals were kept at room temperature (22˚C ± 2˚C).

2.3. Plant Extract Preparation

Momordica foetida leaves, once collected from apical parts of many plants, were

dried at room temperature and then ground to powder. Two hundred and fifty grams of powder were macerated in 250 mL of methanol over 48 hours, filtered through Whatman paper N˚1 and further concentrated using rotary evaporator at 65˚C. The extract obtained was placed in an oven along 48 hours at 40˚C to remove residual solvent, then weighed and stored at 4˚C.

2.4. Acute Toxicity Study

The oral acute toxicity of *Momordica foetida* leaf extract was performed according to OCDE protocols [14]. Ten rats were divided into two groups of 5 animals each: a control group and a test group. The animals were fasted 15 hours prior to their treatment, then weighed before being treated by esophageal gavage. Animals in the control group received 5% Dimethylsulfoxide (DMSO) and those of the test group were administered a unique dose of *M. foetida* extract at 5000 mg/kg b.w. These animals were fasted for additional 3 hours, a period during which signs of toxicity including sensitivity to pain, sensitivity to noise, the tail state, stool appearance and mobility were noted. Furthermore, death was monitored until the fourteenth day post-administration. Finally, animals were euthanized at the end to detect any macroscopic pathological change on organs such as liver, kidneys, lungs or heart by comparing the test animals' organs to control ones [15].

2.5. Sub-Acute Toxicity Study

2.5.1. Experimental Design

The sub-acute toxicity study was conducted according to the OCDE guidelines [16]. Briefly, 40 rats including 20 males and 20 females were each divided into 5 groups of 4 animals each: The control group (Group I) received 5% DMSO; Group II and Group III received 250 and 500 mg/Kg b.w dosages of the plant extract respectively. Group IV and Group V received 1000 mg/Kg b.w of extract. The administration was done daily over a period of 28 days by esophageal gavage for Group I to Group V. At the end of the administration period, Group V (satellite) animals were fed under the same conditions for additional 15 days and monitored along that period. During the experiment, animals were weighed every two days and signs of toxicity were checked on a weekly basis.

2.5.2. Sample Preparation

Animals were subjected to 24 hours food and water fasting along which their urine was collected, centrifuged at 3000 rpm for 10 minutes and stored at −80˚C. They were further anesthetized intraperitoneally with ketamine (50 mg/kg) and their blood was collected into EDTA and dry tubes by cardiac puncture. The blood in dry tubes was allowed to clot for 6 hours then centrifuged at 3000 rpm for 15 minutes. The serum was removed and stored at −80˚C for biochemical assays. Animals were further dissected and organs such as liver, heart, kidneys, lungs, testis and ovaries were collected, weighed and their relative weights were evaluated. A part of each organ was used for protein analysis and other part was maintained

in 9% formalin-NaCl solution until histological analysis.

2.5.3. Hematological Analysis

Hematological parameters: white blood cells, red blood cells, hematocrit, platelets, hemoglobin, granulocytes, lymphocytes, mid-cells, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and Mean Corpuscular Volume (MCV) were analyzed using automaton hematology (PENTRA × 80).

2.5.4. Biochemical Parameters Analysis

Biochemical parameters including creatinine, glucose, proteins, ALT, AST, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, total bilirubin and urea levels were analyzed in serum while urea, creatinine, glucose and protein concentration were also evaluated in urine. These analyses were performed using commercial kits (Hospitex Diagnostics STD, Roma, Italia).

2.5.5. Histological Analysis

The analysis was performed on selected vital organs (liver, kidneys, heart, lungs, testes and ovaries). After euthanasia, all animals were autopsied and the major organs were surgically removed and fixed in 10% formalin in normal saline. Sections of 5 µm were obtained on a rotary microtome, and then, the material was stained by Hematoxylin-Eosin (HE) [17]. The stained slides of the organ sections of the 40 tested animals were analyzed using a microscope with an integrated digital photocamera (EVOS XL, USA) under a magnification objective of 40× for eventual anomalies. The histology of treated groups was compared to control animals' one. After examination, photomicrographs of selected organs were taken, representing the general appearance in at least three of the four animals in the group.

2.5.6. Ethical Considerations

Experimental protocols used in this study strictly conformed with the internationally accepted standard ethical guidelines for laboratory animal use and care as described in the European Community guidelines, EEC Directive 86/609/EEC of the 24th November 1986 [18]. This study was approved by the Institutional Animal Ethics Committee (Registration No. 778/PO/a/03/CPCSEA; 03.09.).

2.5.7. Statistical Analysis

For each parameter, the one-way ANOVA was used to detect significant differences between groups, followed by Dunnett test for multiple comparisons using GraphPad Prism software version 5.00; the results were expressed as mean ± Standard Deviation (SD) with a significance threshold of $p < 0.05$.

3. Result

3.1. Acute Oral Toxicity

During the acute toxicity study, there was no mortality recorded in animals after receiving a single dose of 5000 mg/kg body weight of *Momordica foetida* leaf

methanol extract. Also, no sign of toxicity in general appearance (reduction of locomotion, stool appearance, drowsiness, salivation, reaction to noise) was noticed throughout the experimental period (Table 1). Based on the OECD principle, it can be stated that the LD50 of the methanol extract is greater than 5000 mg/kg b.w.

3.2. Sub-Acute Toxicity

3.2.1. Body Weight and Food Consumption

1) Body weight

The leaf extract of *Momordica foetida* caused no sex-dependent significant change in the parameter in treated animals as compared to controls. The results of the body weight evolvements are summarized in Figure 1 and Figure 2. After the administration period, an increase in rats' body weights was noticed in all groups. Compared to the control group, a significant increase was observed in body weights of male rats treated with the extract (1000 mg/kg and satellite) on the 12th, the 16th and the 24th days. In female rats, a significant decrease was observed in body weight ($p < 0.001$) of all groups treated from the 8th to the 24th day of experiment. The 28th day, a decrease in weight gain was observed at doses 500 mg/kg and 1000 mg/kg, while in rats of the satellite group and those treated at 250 mg/kg dosage, no significant difference was observed.

2) Food consumption

The food consumption patterns of female and male rats treated with different doses (250, 500, and 1000 mg/kg body weight) of the extract are presented in Figure 3 and Figure 4. Males' rats recorded a significant decrease in food intake comparatively to the control on days 8 and 24 of treatment at the highest dose. In females, a significant decrease was recorded in food intake of rats treated with 250 mg/kg and 500 mg/kg b.w dosages during the 4th, 8th, 20th and 24th days of experimentation.

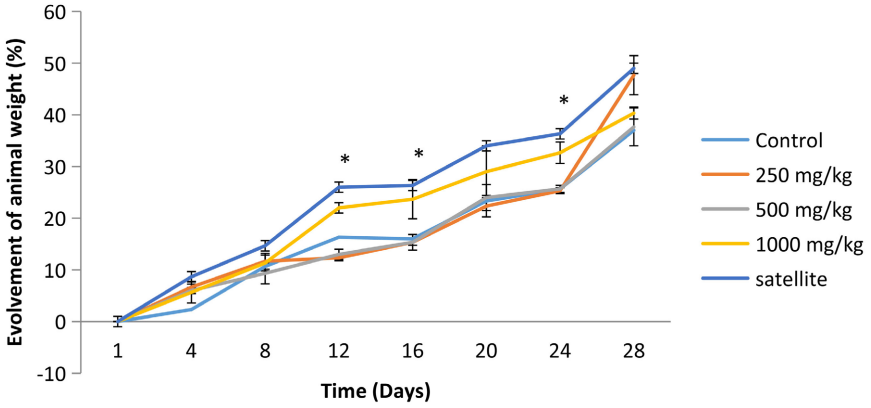

Figure 1. Evolvement of the body weight gain of the male rats during the administration period. Each curve represents the mean ± s.e.m. of the values for 4 animals. The values presented are the means of the percentage's values of the body weight of each animal relatively to the starting weight. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test).

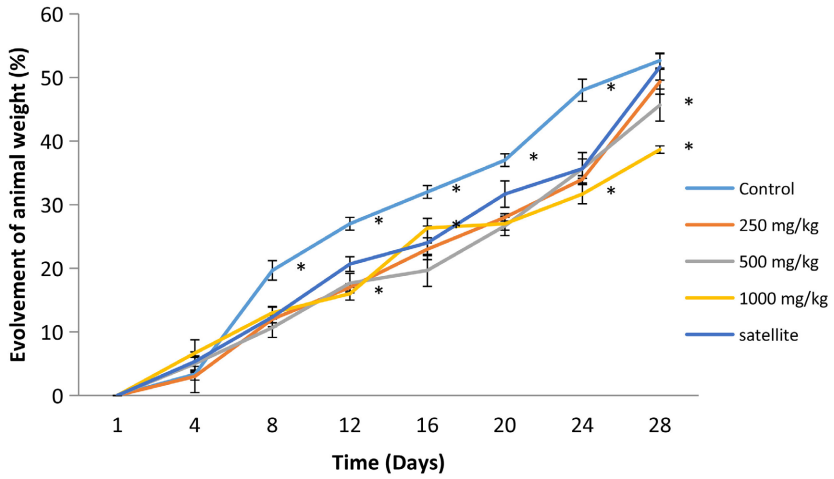

Figure 2. Evolvement of the body weight gain of the female rats during the administration period. Each curve represents the mean ± s.e.m. of the values for 4 animals. The values presented are the means of the percentage's values of the body weight of each animal relatively to the starting weight. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test).

Table 1. Acute toxicity study of methanol extract of *Momordica foetida* in female rates.

	Female		
Time	1 hour	2 hours	3 hours
Reaction to pain	N	N	N
Locomotion	N	N	N
Grouping	N	N	N
Aggressiveness	N	N	N
Appearance of faeces	N	P	P
Reaction to noises	N	N	N
Number of dead	0	0	0

N: Normal, P: Pasty.

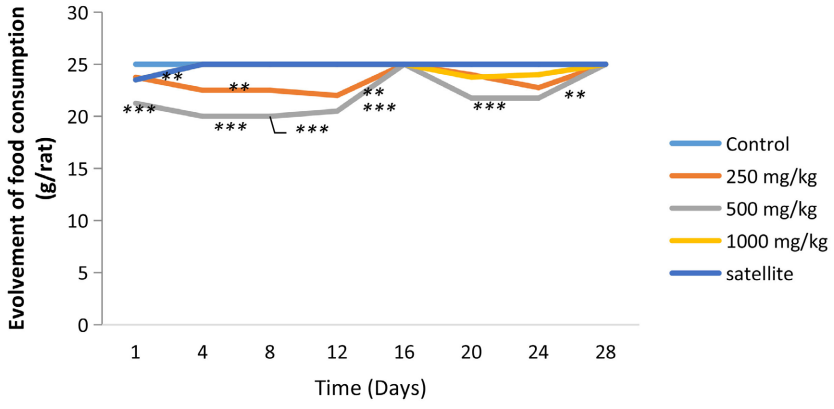

Figure 3. Effect of subacute administration of methanol extract of *M. foetida* on food consumption of male rats. Data are expressed as mean ± SD, n = 4.*, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test).

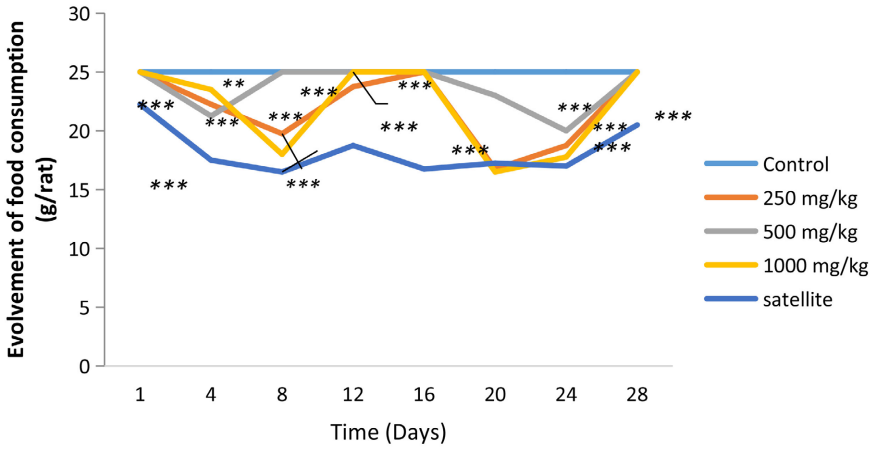

Figure 4. Effect of subacute administration of methanol extract of *M. foetida* on food consumption of female rats. Data are expressed as mean ± SD, n = 4.*, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test).

3.2.2. Relative Organ Weight

Momordica foetida methanol extract revealed no change in the relative weight of heart, lung and ovaries/testes in animals (Table 2). Significant change ($p < 0.05$) was instead observed in the relative weight of the spleen of male rats treated at the dose of 1000 mg/kg b.w. In females, weight loss was observed in liver and kidneys respectively at the doses of 250 mg/kg and 500 mg/kg b.w.

3.2.3. Hematological Parameters

The hematological profile of the rats treated with different doses of *Momordica foetida* is presented in Table 3 and Table 4. Significant increase ($p < 0.05$) in the mean levels of red blood cells, platelets, hemoglobin and granulocytes was found in both sexes. However, no effect on RDW-CV (Red Cell Distribution Width Cell Volume), RDW-SD (Red Cell Distribution Width Standard Deviation), MPV (Mean Platelet Volume) and P-LCR (Platelet Large Cell Ratio) regardless of doses and sex was observed. Particularly, a significant increase was observed in mean levels of white blood cells, PDW (Platelet Distribution Width), P-LCC (Platelet Large Cell Count) in male rats. Significant increase in MID or MCHC (mean corpuscular hemoglobin concentration) and significant decrease in mean levels of lymphocytes and MCV (Mean Cell Volume) were also recorded in female rats.

3.2.4. Biochemical Parameters

The effect of *Momordica foetida* leaf extract on biochemical parameters is presented in Tables 5-8. The extract induced an increase in total cholesterol, HDL cholesterol and decreased the mean levels of LDL-cholesterol independently of sex and doses. No effect on the mean levels of triglycerides was noticed in male rats and significant decrease was observed in female ones (Table 5). A significant decrease ($p < 0.05$) in serum concentration of AST, ALT and proteins was observed in both sexes. However, no effect was observed in total bilirubin concentration (Table 6).

Table 2. Relative organ weights of rats in sub-acute toxicity of the methanol extract of *M. foetida*.

Sex	Doses (mg/Kg)	Liver	Kidneys	Heart	Lungs	Spleen	Teste/Ovaries
Male	Control	2.72 ± 0.24	0.48 ± 0.07	0.26 ± 0.03	0.55 ± 0.16	0.20 ± 0.06	1.01 ± 0.17
	250	2.66 ± 0.19^{ns}	0.47 ± 0.03^{ns}	0.26 ± 0.03^{ns}	0.53 ± 0.23^{ns}	0.29 ± 0.06^{ns}	1.02 ± 0.1^{ns}
	500	2.71 ± 0.29^{ns}	0.48 ± 0.03^{ns}	0.29 ± 0.04^{ns}	0.59 ± 0.03^{ns}	0.20 ± 0.03^{ns}	1.14 ± 0.08^{ns}
	1000	2.64 ± 0.28^{ns}	0.54 ± 0.03^{ns}	0.25 ± 0.02^{ns}	0.57 ± 0.05^{ns}	0.44 ± 0.13*	1.19 ± 0.12^{ns}
	Satellite	2.61 ± 0.65^{ns}	0.50 ± 0.09^{ns}	0.28 ± 0.06^{ns}	0.69 ± 0.19^{ns}	0.22 ± 0.02^{ns}	1.3 ± 0.26^{ns}
Female	Control	2.94 ± 0.38	0.55 ± 0.01	0.26 ± 0.02	0.55 ± 0.05	0.17 ± 0.00^{ns}	0.02 ± 0.00
	250	2.18 ± 0.23*	0.47 ± 0.02^{ns}	0.27 ± 0.02^{ns}	0.61 ± 0.1^{ns}	0.18 ± 0.05^{ns}	0.02 ± 0.00^{ns}
	500	2.21 ± 0.24*	0.49 ± 0.06^{ns}	0.25 ± 0.02^{ns}	0.55 ± 0.03^{ns}	0.21 ± 0.02^{ns}	0.03 ± 0.00^{ns}
	1000	2.26 ± 0.18^{ns}	0.45 ± 0.04*	0.25 ± 0.00^{ns}	0.64 ± 0.1^{ns}	0.17 ± 0.01^{ns}	0.02 ± 0.00^{ns}
	Satellite	2.68 ± 0.57^{ns}	0.51 ± 0.01^{ns}	0.29 ± 0.02^{ns}	0.61 ± 0.06^{ns}	0.21 ± 0.03^{ns}	0.02 ± 0.00^{ns}

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant.

Table 3. Effect of methanol extract of *M. foetida* on hematological parameters of treated male rats.

	Dose (mg/kg)	Control	250	500	1000	Satellite
Male	WBC (10^3/µL)	8.87 ± 0.06	6.82 ± 0.93^{ns}	14.29 ± 2.90***	9.05 ± 1.19^{ns}	4.30 ± 0.19***
	RBC (10^6/µL)	6.29 ± 0.22	7.10 ± 0.31**	6.55 ± 0.45^{ns}	6.15 ± 0.15^{ns}	7.56 ± 0.25***
	Hematocrit (%)	44.35 ± 1.99	44.83 ± 2.42^{ns}	42.07 ± 4.00^{ns}	39.33 ± 0.46^{ns}	47.73 ± 2.81^{ns}
	Platelets (10^3/µL)	722.00 ± 49.30	771.30 ± 54.14^{ns}	689.00 ± 48.15^{ns}	874.8 ± 11.95*	827.00 ± 123.2^{ns}
	Haemoglobin (g/dL)	12.63 ± 0.89	14.20 ± 0.86*	12.88 ± 0.38^{ns}	12.78 ± 0.60^{ns}	14.48 ± 0.39**
	Granulocytes (%)	18.90 ± 1.49	19.68 ± 0.61^{ns}	20.81 ± 3.11^{ns}	24.58 ± 2.77*	15.90 ± 3.39^{ns}
	Lymphocytes (%)	76.98 ± 1.72	76.18 ± 0.69^{ns}	77.58 ± 6.04^{ns}	74.60 ± 9.71^{ns}	83.93 ± 6.27^{ns}
	MID (%)	3.77 ± 0.57	4.77 ± 0.28^{ns}	4.9 ± 1.36^{ns}	5.32 ± 0.95^{ns}	2.72 ± 0.23^{ns}
	MCHC(g/dl)	31.98 ± 0.35	31.70 ± 0.49^{ns}	30.77 ± 1.88^{ns}	30.83 ± 4.35^{ns}	30.70 ± 0.78^{ns}
	MCV	62.25 ± 0.96	62.43 ± 2.65^{ns}	63.17 ± 0.81^{ns}	63.43 ± 1.66^{ns}	64.68 ± 3.32^{ns}
	MCH	19.75 ± 0.31	18.83 ± 0.33^{ns}	19.83 ± 0.74^{ns}	20.38 ± 0.42^{ns}	20.40 ± 1.39^{ns}
	RDW-CV	16.08 ± 1.57	16.05 ± 0.12^{ns}	16.68 ± 0.77^{ns}	15.40 ± 0.65^{ns}	16.85 ± 0.53^{ns}
	RDW-SD	32.20 ± 3.05	33.10 ± 2.32^{ns}	32.16 ± 0.57^{ns}	31.60 ± 2.17^{ns}	35.83 ± 2.46^{ns}
	MPV	8.17 ± 0.12	8.25 ± 0.83^{ns}	8.17 ± 0.41^{ns}	8.62 ± 0.47^{ns}	8.27 ± 0.53^{ns}
	PDW	15.48 ± 0.20	15.60 ± 0.15^{ns}	16.05 ± 0.19**	15.85 ± 0.12*	16.15 ± 0.26***
	PCT	0.60 ± 0.06	0.58 ± 0.11^{ns}	0.60 ± 0.14^{ns}	0.74 ± 0.07^{ns}	0.65 ± 0.10^{ns}
	P-LCC	157.3 ± 16.68	141.00 ± 10.07^{ns}	151.30 ± 7.76^{ns}	187.80 ± 12.37**	153.00 ± 10.68^{ns}
	P-LCR	16.23 ± 1.11	18.28 ± 5.49^{ns}	17.23 ± 2.69^{ns}	19.68 ± 3.54^{ns}	17.98 ± 4.11^{ns}

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant. WBC: White Blood Cells; RBC: Red Blood Cells; MID: Mid-Cells; MCHC: Mean Cell Haemoglobin Concentration; MCV: Mean Cell Volume; MCH: Mean Cell Haemoglobin; RDW-CV: Red Cell Distribution Width Cell Volume; RDW-SD: Red Cell Distribution Width Standard Deviation; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; PCT: Platelet Count (%); P-LCR: Platelet Large Cell Ratio; P-LCC: Platelet Large Cell Count.

Table 4. Effect of methanol extract of *M. foetida* on hematological parameters of treated female rats.

	Dose (mg/kg)	Control	250	500	1000	Satellite
Female	WBC (10^3/µL)	7.36 ± 0.67	6.78 ± 1.06^{ns}	9.91 ± 1.27^{ns}	9.73 ± 2.42^{ns}	3.31 ± 0.18**
	RBC (10^6/µL)	6.01 ± 0.07	6.69 ± 0.48*	6.34 ± 0.17^{ns}	6.29 ± 0.19^{ns}	6.57 ± 0.35^{ns}
	Hematocrit (%)	44.50 ± 4.65	42.68 ± 2.80^{ns}	40.20 ± 1.41^{ns}	39.83 ± 1.20^{ns}	43.57 ± 1.27^{ns}
	Platelets (10^3/µL)	690.00 ± 105.4	846.00 ± 89.71*	874.00 ± 71.05*	937.80 ± 58.04**	839.80 ± 59.25^{ns}
	Haemoglobin (g/dL)	12.50 ± 0.29	13.63 ± 0.74*	13.20 ± 0.40^{ns}	13.20 ± 0.40^{ns}	13.58 ± 0.51*
	Granulocytes (%)	7.77 ± 0.28	21.20 ± 2.84***	15.98 ± 0.65***	22.80 ± 3.44***	8.00 ± 0.21^{ns}
	Lymphocytes (%)	95.60 ± 2.44	74.40 ± 3.17***	83.20 ± 3.75***	75.68 ± 7.94***	91.48 ± 0.28^{ns}
	MID (%)	1.35 ± 0.56	4.40 ± 0.48***	3.05 ± 0.10***	5.02 ± 0.66***	0.95 ± 0.12^{ns}
	MCHC (g/dl)	29.78 ± 2.87	31.90 ± 0.64^{ns}	32.87 ± 0.20*	3.23 ± 0.69^{ns}	32.03 ± 0.26^{ns}
	MCV (fl)	78.60 ± 1.84	64.90 ± 5.02***	77.15 ± 1.14^{ns}	61.07 ± 1.85***	64.03 ± 0.61***
	MCH (pg)	20.80 ± 0.50	20.30 ± 0.82^{ns}	20.45 ± 0.23^{ns}	19.65 ± 0.20*	20.80 ± 0.50^{ns}
	RDW-CV (%)	19.30 ± 1.53	17.58 ± 1.72^{ns}	18.28 ± 2.70^{ns}	16.53 ± 1.03^{ns}	16.50 ± 0.64^{ns}
	RDW-SD (fl)	33.78 ± 2.40	32.83 ± 1.02^{ns}	31.50 ± 1.22^{ns}	33.00 ± 2.56^{ns}	35.35 ± 2.13^{ns}
	MPV (fl)	7.80 ± 0.86	7.77 ± 0.46^{ns}	7.45 ± 0.64^{ns}	7.95 ± 0.71^{ns}	7.92 ± 0.50^{ns}
	PDW (fl)	16.03 ± 0.09	15.70 ± 0.08*	15.95 ± 0.26^{ns}	15.70 ± 0.08*	15.98 ± 0.17^{ns}
	PCT (%)	0.53 ± 0.09	0.65 ± 0.11^{ns}	0.59 ± 0.13^{ns}	0.49 ± 0.12^{ns}	0.72 ± 0.11^{ns}
	P-LCC	130.30 ± 21.42	109.00 ± 22.46^{ns}	126.30 ± 3.09^{ns}	119.3 ± 10.63^{ns}	137.80 ± 7.71^{ns}
	P-LCR	16.23 ± 1.11	18.28 ± 5.49^{ns}	17.23 ± 2.69^{ns}	19.68 ± 3.54^{ns}	17.98 ± 4.11^{ns}

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant. WBC: White Blood Cells; RBC: Red Blood Cells; MID: Mid-Cells; MCHC: Mean Cell Haemoglobin Concentration; MCV: Mean Cell Volume; MCH: Mean Cell Haemoglobin; RDW-CV: Red Cell Distribution Width Cell Volume; RDW-SD: Red Cell Distribution Width Standard Deviation; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; PCT: Platelet Count (%); P-LCR: Platelet Large Cell Ratio; P-LCC: Platelet Large Cell Count.

Table 5. Lipid parameters of rats administered the methanol leaf extract of *M. foetida* in sub-acute toxicity assay.

Sex	Dose (mg/kg)	TC (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	LDL-C (mg/dl)	AI
Males	Control	114.5 ± 0.85	46.29 ± 0.87	71.33 ± 0.19	53.46 ± 0.42	1.58 ± 0.13
	250	99.70 ± 2.01***	53.18 ± 0.52***	73.33 ± 0.38*	32.40 ± 1.53***	0.88 ± 0.02***
	500	103.0 ± 1.91***	51.97 ± 0.52***	72.76 ± 0.31^{ns}	36.75 ± 2.53***	0.99 ± 0.07***
	1000	102.0 ± 3.87***	50.91 ± 0.55***	71.43 ± 0.38^{ns}	38.22 ± 1.65***	1.00 ± 0.06***
	Satellite	95.15 ± 0.85***	41.59 ± 1.40***	72.89 ± 2.07^{ns}	38.86 ± 2.55***	1.29 ± 0.07**
Females	Control	112.1 ± 2.57	45.45 ± 1.83	71.90 ± 0.36	49.67 ± 1.79	1.46 ± 0.05
	250	102.7 ± 0.34***	50.61 ± 0.24***	61.33 ± 1.20***	39.72 ± 0.45***	0.95 ± 0.13***
	500	97.73 ± 3.97***	50.53 ± 0.67***	68.10 ± 1.36***	35.64 ± 1.56***	0.84 ± 0.11***
	1000	96.97 ± 1.48***	48.56 ± 1.27**	71.52 ± 1.25^{ns}	35.47 ± 1.50***	0.98 ± 0.11***
	Satellite	95.15 ± 0.49***	41.67 ± 1.00**	69.33 ± 0.69*	39.62 ± 0.88***	1.28 ± 0.05^{ns}

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant TC: Total Cholesterol; HDL-C: HDL-Cholesterol; LDL-C: LDL-Cholesterol. AI: Artherogenic Index.

Table 6. Transaminases activity, bilirubin and serum protein concentrations variations in rats treated with methanol leaf extract of *M. foetida* through sub-acute toxicity test.

Sex	Dose (mg/kg)	ALT (U/L)	AST (U/L)	Bilirubin (mg/dl)	Serum proteins (mg/dl)
Males	Control	12.47 ± 1.36	52.39 ± 7.93	0.02 ± 0.01	5.92 ± 0.28
	250	6.92 ± 1.33***	47.86 ± 7.48ns	0.00 ± 0.00ns	5.12 ± 0.04***
	500	6.52 ± 1.62***	31.11 ± 4.32***	0.00 ± 0.00ns	5.06 ± 0.04***
	10000	4.67 ± 0.82***	35.75 ± 3.00**	0.00 ± 0.00ns	5.15 ± 0.04***
	Satellite	12.06 ± 2.33ns	27.58 ± 3.94***	0.00 ± 0.00ns	5.25 ± 0.05***
Females	Control	10.36 ± 1.44	44.64 ± 1.48	0.00 ± 0.00	5.55 ± 0.04
	250	4.80 ± 0.87***	27.14 ± 3.57***	0.00 ± 0.00ns	5.12 ± 0.03***
	500	5.55 ± 0.85***	28.53 ± 1.72***	0.00 ± 0.00ns	5.03 ± 0.04***
	1000	5.86 ± 0.82***	29.41 ± 3.12***	0.00 ± 0.00ns	5.05 ± 0.02***
	Satellite	9.84 ± 1.82ns	22.02 ± 3.18***	0.00 ± 0.00ns	5.20 ± 0.01***

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant.

Table 7. Renal parameters in sub-acute toxicity with methanol leaf extract of *M. foetida*.

Sex	Dose (mg/kg)	Urinary protein (mg/dl)	Serum urea (mg/dl)	Urinary urea (mg/dl)	Serum creatinine (mg/dl)	Urinary creatinine (mg/dl)
Males	Control	4.61 ± 0.13	46.62 ± 2.54	1249 ± 89.81	78.00 ± 4.00	0.47 ± 0.09
	250	5.41 ± 0.12***	60.81 ± 3.19***	765.4 ± 5.15***	60.50 ± 3.41***	0.42 ± 0.05 ns
	500	5.10 ± 0.04***	64.21 ± 3.47***	845.3 ± 28.27***	37.50 ± 3.78***	0.45 ± 0.10 ns
	1000	5.20 ± 0.03***	72.44 ± 1.89***	1045 ± 81.35***	21.00 ± 3.83***	0.40 ± 0.00 ns
	Satellite	5.28 ± 0.09***	75.00 ± 0.55***	1488 ± 26.56***	85.00 ± 3.83ns	0.42 ± 0.12 ns
Females	Control	6.11 ± 0.04	44 .48 ± 3.14	1324 ± 88.09	90.75 ± 3.59	1.42 ± 0.17
	250	5.25 ± 0.06***	53.51 ± 4.56**	1023 ± 23.78***	64.00 ± 3.26***	0.42 ± 0.05***
	500	5.25 ± 0.03***	55.65 ± 0.90***	1067 ± 51.45***	32.75 ± 1.50***	0.52 ± 0.15***
	1000	5.38 ± 0.06***	56.56 ± 1.69***	1327 ± 78.29ns	25.75 ± 1.70***	1.65 ± 0.10ns
	Satellite	5.11 ± 0.07***	72.75 ± 3.37***	1457 ± 38.99*	88.75 ± 6.70ns	2.22 ± 0.17***

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant.

Table 8. Serum and urinary glucose of rats in sub-acute toxicity trials with methanol leaf extract of *M. foetida*.

Sex	Dose (mg/kg)	Serum glucose (mg/dl)	Urinary glucose (mg/dl)
Males	Control	101.00 ± 1.08	102.1 ± 1.95
	250	102.9 ± 1.84ns	108.5 ± 1.62***
	500	105.5 ± 0.40***	110.3 ± 1.95***
	1000	103.9 ± 0.85*	103.3 ± 2.14ns
	Satellite	96.50 ± 1.68***	59.40 ± 1.73***
Females	Control	99.88 ± 0.25	95.08 ± 2.28
	250	103.8 ± 0.50**	102.6 ± 0.62*
	500	103.8 ± 0.64**	103.9 ± 2.98**
	1000	101.4 ± 1.10ns	99.43 ± 5.43ns
	Satellite	97.50*	57.09 ± 1.72***

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant.

Serum urea as well as serum and urinary glucose were significantly increased in both rats' sexes after oral administration of different doses of *Momordica foetida* extract along 28 days (Table 7 and Table 8). Significant decrease of urinary proteins as well as serum and urinary urea were also noted on both sexes. No effect was observed in mean levels of urinary creatinine in male rats but a significant decrease was noticed in females at 250 mg/kg and 500 mg/kg b.w. dosages.

The effect of prolonged administration of the extract on organs protein levels is shown in Table 9. Analysis of this table shows a decrease ($p < 0.05$) in kidneys and testes protein levels in treated male animals at all doses in kidneys and the dose of 500 - 1000 mg/kg in testes. However, a significant increase ($p < 0.05$) was observed in female liver (1000 mg/kg) and kidney (500 mg/kg) protein levels while a significant decrease was registered in protein levels in lung (500 mg/kg) and ovary (250 mg/kg) as compared to controls.

3.2.5. Histological Analysis

Histological examination was performed on six vital organs (liver, kidneys, heart, lung ovaries and testes) to evaluate the extent of tissues damage. Conventional light microscopy photographs of male and female rat's organ sections are shown in Figures 5-9. No abnormal morphology and histological lesions were found in the organs of treated rats compared to those of the control group.

4. Discussion

The acute-toxicity study demonstrated that the 5000 mg/kg b.w. oral dose of *Momordica foetida* extract did not cause any toxicity symptoms or mortality in female rats. There was no significant difference in body weight between treated groups and the control. This result showed that LD50 of *Momordica foetida* leaf extract was higher than 5000 mg/kg, indicating that this extract may be estimated nontoxic. Accordingly, the crude extract of *Momordica foetida* was assigned class

Table 9. Effect of *M. foetida* leaf extract on animals' organs proteins.

Sex	Dose (mg/kg)	Liver (mg/g)	Kidneys (mg/g)	Heart (mg/g)	Lungs (mg/g)	Testes/Ovaries (mg/g)
Males	Control	52.97 ± 0.39	54.87 ± 0.39	51.39 ± 0.15	51.00 ± 0.54	51.47 ± 0.25
	250	52.50 ± 1.46^{ns}	52.66 ± 0.53***	51.95 ± 0.54^{ns}	52.58 ± 0.94^{ns}	50.21 ± 0.25^{ns}
	500	52.97 ± 0.83^{ns}	53.37 ± 0.44**	50.84 ± 0.44^{ns}	51.47 ± 2.20^{ns}	48.79 ± 1.27**
	1000	52.74 ± 0.57^{ns}	53.13 ± 0.59***	50.53 ± 1.34^{ns}	51.08 ± 0.83^{ns}	46.97 ± 0.53***
	Satellite	49.66 ± 0.15^{ns}	50.29 ± 0.30***	51.00 ± 0.18^{ns}	51.08 ± 0.15^{ns}	52.03 ± 1.42^{ns}
Females	Control	53.84 ± 1.10	52.34 ± 0.39	51.71 ± 0.39	51.71 ± 0.47	50.29 ± 0.83
	250	53.29 ± 0.53^{ns}	52.89 ± 0.65^{ns}	50.29 ± 1.37^{ns}	51.24 ± 0.53^{ns}	45.79 ± 0.00**
	500	53.29 ± 0.53^{ns}	53.53 ± 0.98*	50.29 ± 1.19^{ns}	50.68 ± 0.40*	47.92 ± 2.63^{ns}
	1000	51.83 ± 0.60**	53.13 ± 0.47^{ns}	49.97 ± 0.94^{ns}	50.76 ± 0.70^{ns}	48.55 ± 0.70^{ns}
	Satellite	50.84 ± 0.44***	50.05 ± 0.18***	51.08 ± 0.65^{ns}	50.53 ± 0.25*	53.03 ± 1.42^{ns}

Data are expressed as mean ± SD, n = 4. *, **, *** indicate a significant difference at $p < 0.05$. $p < 0.01$ and $p < 0.001$ respectively, compared to the control group (Dunnett's test). ns: non-significant.

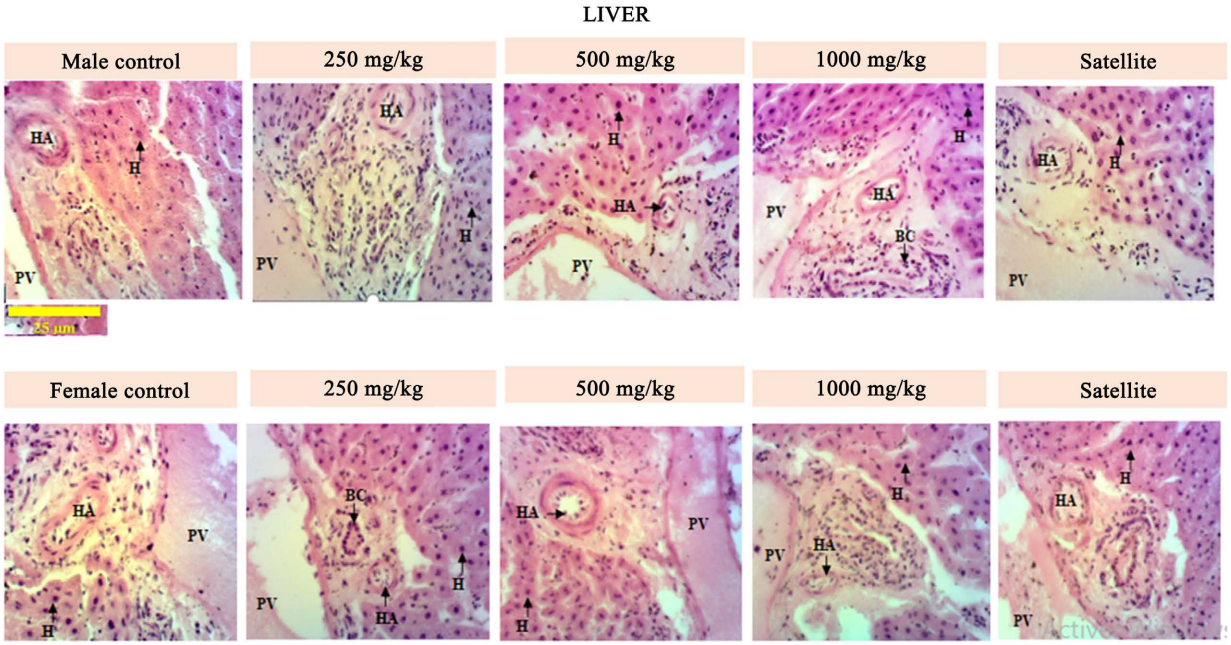

Figure 5. Histology of male and female rat's liver exposed to sub-acute oral treatment of *M. foetida* methanol leaf extract. HA: Hepatic Artery; H: Hepatocyte; PV: Hepatic Portal vein; BC: Bile Canaliculus.

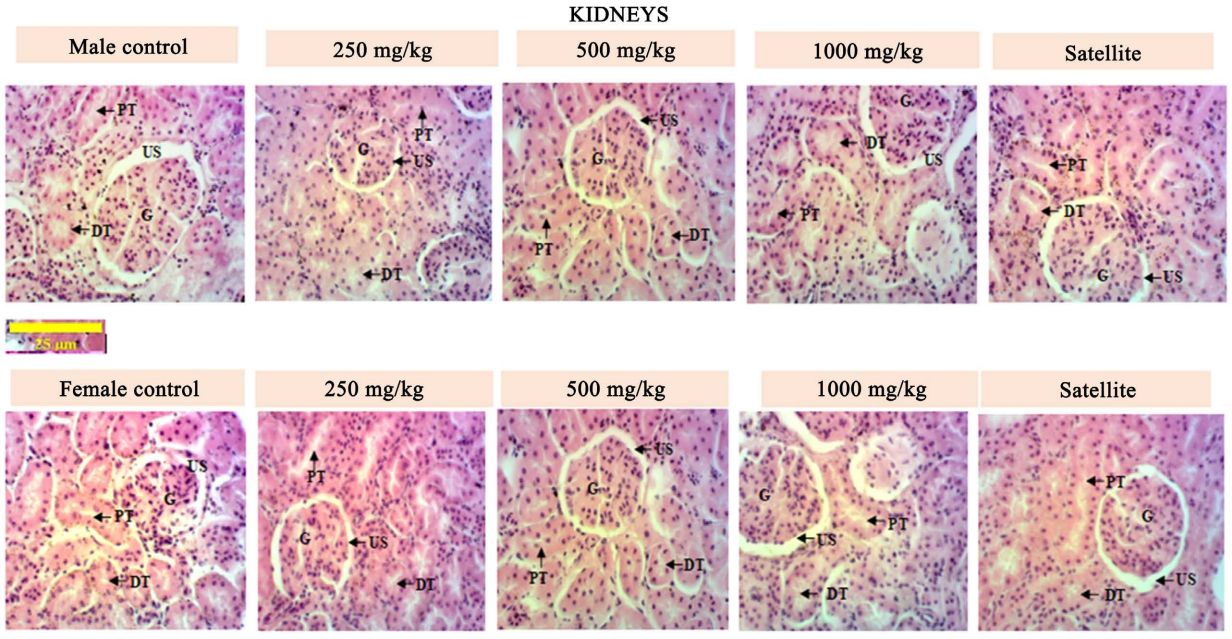

Figure 6. Histology of male and female rat's kidneys exposed to sub-acute oral treatment of *M. foetida* methanol leaf extract. PT: Proximal Convoluted Tubule; US: Urinary Space; DT: Distal Convoluted Tubule; G: Glomeruli.

5 status (LD50 > 5000 mg/kg) under the chemical labelling and classification of acute systemic toxicity recommended by OECD [14], which is the lowest toxicity class. Since no toxic effects was found during the acute toxicity trials, further study was conducted to evaluate the sub-acute toxicity of the extract over consecutive 28 days administration to prepare inclusive toxicological records on this plant.

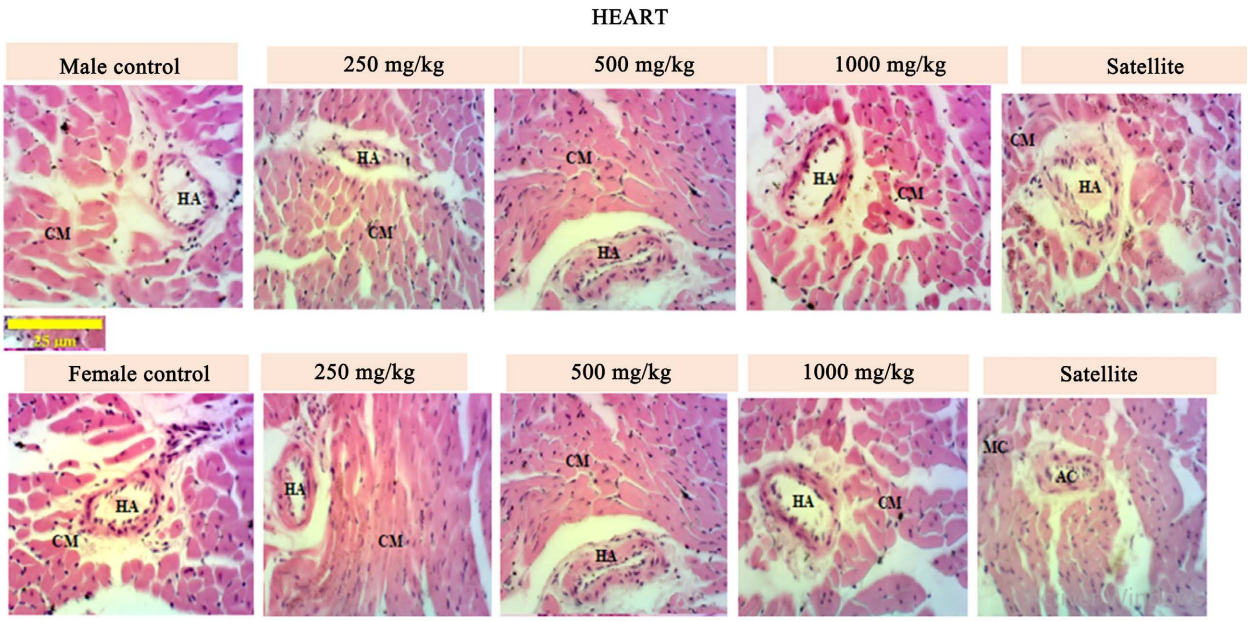

Figure 7. Histology of male and female rat's heart exposed to sub-acute oral treatment of *M. foetida* methanol leaf extract. CM: Cardiac Myocyte; HA: Branch of a Heart Artery.

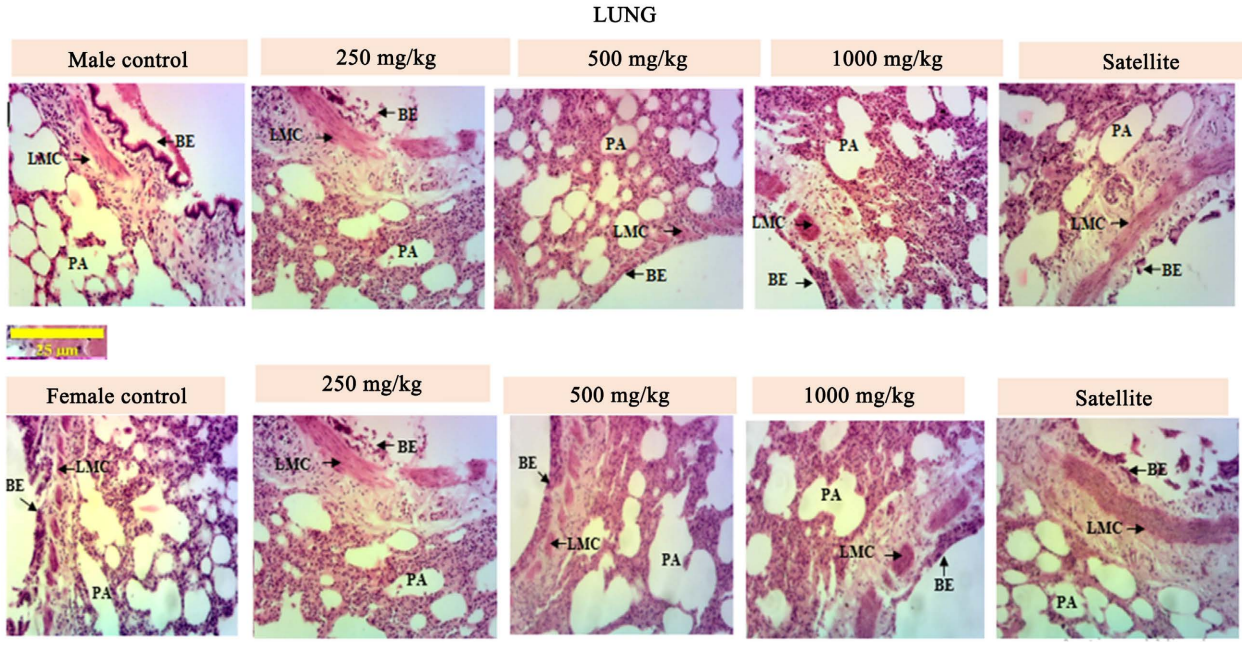

Figure 8. Histology of male and female rat's lung exposed to sub-acute oral treatment of *M. foetida* methanol leaf extract. LMC: Layers of Smooth Muscle Cells; BE: Bronchial Epithelium; PA: Pulmonary Alveoli.

Repeated administration of 250, 500 and 1000 mg/Kg b.w doses of the extract showed some variation ($p < 0.05$) in weight gain and food consumption. During the toxicity studies, the body weight changes serve as a sensitive indication of the general health status of animals while the food intake is used as indicator of their metabolism [19]. An increase in rats' male body weights gain noticed in all groups suggest that the leaves methanol extract of *Momordica foetida* did not

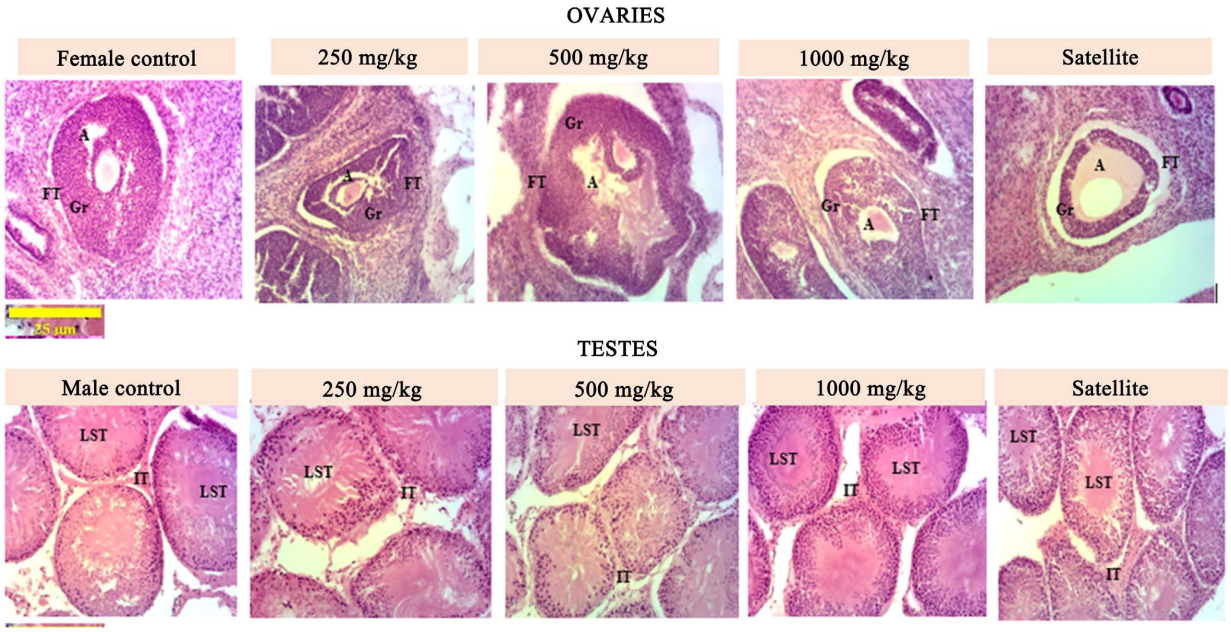

Figure 9. Histology of ovaries and testes rats exposed to sub-acute oral treatment of *M. foetida* methanol leaf extract. A: Antrum; Gr: Granulosa; FT: Follicular Theca; IT: Interstitial tissue; LST: Lumen of Seminiferous Tubule.

interfere with the general health status and the normal metabolism of animals. However, the decrease observed in body weight gain of female rats in all groups treated from the 8th to the 24th day of experiment compared to the control group suggest the negative effect on general health. The decrease of food intake in female rats of all groups treated from the 8th to the 24th day of experiment and 28th day in male rat treated at doses of 500 mg/kg and 1000 mg/kg, may be due to the anorexic effect of the plant extract.

In this study, significant change was observed in the relative weight of the spleen with 1000 mg/kg b.w. dosage-treated male rats. In females, weight loss was experienced in liver and kidneys respectively at the doses of 250 mg/kg and 500 mg/kg b.w. Kidneys and livers are the main organs involved in xenobiotics metabolism. Increase or decrease in the kidneys and liver weights could be correlated to toxic effect of *Momordica foetida* leaf extract but histological sections observation did not reveal any morphological alteration in the organs, then this would be an artefactual observation as changes in the weight of these vital organs, related to toxicity, are frequently accompanied by histopathological modifications. However, changes in the weight of certain organs such as lungs, heart and spleen have less impact on toxicity because of their limited role in eliminating harmful substances from the body [20].

In sub-acute treatment, *Momordica foetida* extract resulted in increase in white blood cells counts at 500 mg/kg in male rats; granulocytes were particularly raised in 1000 mg/kg-treated animals. An increase in these parameters may indicate the activation of the immune system, inflammation, necrosis or a malignant infection [21]. Similar results were observed with lymphocytes, granulocytes and mid-cells on female rats. Lymphocytes are involved in adaptive im-

munity mechanisms; it helps body's immune system to fighting cancer, viruses and bacteria. Granulocytes help the body to fight bacterial infection. Mid-cells are involved in phagocytosis and inflammatory reaction processes [22]. *Momordica foetida* extract could therefore activate innate and adaptive immune response by enhancing any of the steps of the differentiation of these cells or acting directly on the cells.

An increase in red blood cells count was observed in both sexes, showing that the plant extract affects erythropoiesis. Red blood cells are involved in the transport of respiratory gases within the body and in the maintenance of acid-base balance. An increase in their rate could suggest no oxygenation and no anemia risk associated to extract administration [23]. The methanol extract of *Momordica foetida* extract caused an increase in blood platelet levels in both sexes. Platelets are small irregularly shaped fragments which freely circulate in blood. They are involved in the clotting process and their reduction could result in increased bleeding risk [24]. Thus, the methanol extract of *Momordica foetida* could therefore have cicatrizing properties.

A decrease in transaminase activity was recorded with all doses in both sexes. The liver is a central organ for xenobiotic elimination. In case of hepatic injury, there is an increase in transaminase activity (ALT, AST) in the blood due to the release of these enzymes from hepatocytes. Transaminases are tissue enzymes, catalyzing the transport of alpha-amino groups of alanine and aspartic acid to the alpha-ketoglutaric acid which becomes glutamic acid. These enzymes are synthesized in the cytoplasm and released into circulation when cells are damaged [25]. ALT is more specific to liver damage, while the AST is slightly more sensitive [26]. The decrease in serum transaminase level obtained through the present study could reflect no deleterious effect of the methanol extract of *Momordica foetida* on hepatic function. This indicates that liver damage caused by this extract cannot be suspected; however, the extract may help liver in its function by decreasing it activity. These results are in agreement with Metoh and collaborators [10] who shown no significant difference in serum transaminase enzymes levels when the extract was orally administrated at doses between 1530.3 and 2260.7 mg/kg b.w. The unaffected state of the liver after extract administration is confirmed by histopathological analysis which revealed no lesions at all treatment dosages both in males and females.

Bilirubin is a yellow pigment which results from degradation of hemoglobin and other heme proteins (cytochromes, catalase…). Its abnormal accumulation in blood and tissues leads to jaundice. In this study, no significant change was observed in rats' levels independently of sex and dose of the plant extract used. The results obtained fit with the non-hepatotoxic effect previously mentioned. The results were identical to those reported by Wan-yu and collaborators [27] who found no significant difference in serum bilirubin activity when administering aqueous seed-extract of *Momordica charantia* through sub-acute *per os* treatment.

In male rats, triglyceride levels increased at the dose of 250 mg/kg but no sig-

nificant difference was noticed at doses of 500 mg/kg and 1000 mg/kg as compared to control values. Female rats on the contrary experienced decrease in triglyceride levels at all tested doses compared to the control. Total Cholesterol, LDL-Cholesterol and atherosclerosis index were decreased in both sexes while an increase was experienced in HDL-Cholesterol. This result indicates that the extract could have no effect on lipid metabolism. It would therefore present no cardiovascular disease risk. According to Schäffler and Menche [28], excess of "bad" cholesterol (LDL) and lack of "good" cholesterol (HDL) are major risk factors for cardiovascular disease. This hypothesis is supported by the triglyceride level which did not significantly change in the experimental groups as compared to the control. Indeed, higher levels of triglycerides measured in a fasting specimen indicate a lack of clearance or over-production; it could increase the risk of developing cardiovascular disease. The decrease in LDL cholesterol level led by *Momordica foetida* extract confirms the results of Yanmei *et al.* [29] or Hiroki and Yasuyuki [30] which showed that a plant of the same genus *Momordica charantia* is effective against lipid metabolism disorder associated with an increased blood level in Low-Density Lipoprotein (LDL).

Serum urea, serum and urinary creatinine, as well as urinary protein levels are used to evaluate the kidney's function [31]. In the present study, a significant decrease was registered in serum creatinine level of female rats at 250 mg/kg and 500 mg/kg dosages while no significant difference was obtained in other doses and in male treated group. The creatinine is known as an effective indicator of renal function and especially of the glomerular filtration rate. Kidney malfunction causes a rise above the normal threshold of serum creatinine and decrease urinary levels. This result obtained could suggest that the *M. foetida* methanol extract did not affect the renal function. A significant increase in serum urea and significant decrease in urinary urea were noticed in both sexes at all the doses. Kidney's diseases are associated with reduced urea excretion and consequent rise in blood concentration [32]. The increase in serum urea levels and urinary urea levels will be either due to the high content of nitrogenous compounds in the extract or due to the abundance of excreted nitrogenous metabolites, as urea results from the metabolic processes of the ornithine cycle and is the main metabolic pathway for excretion of excess body nitrogen.

The absence of abnormalities in histological sections of gonads (testis and ovaries) reflects no adverse effect of the extract on the reproductive organs and therefore on fertility.

Toxic effects observed in hematological parameters (RBC, hematocrit, platelets, granulocytes, lymphocytes and mid-cells), biochemical parameters (triglycerides, ALT, bilirubin and serum creatinine) and histology of liver and kidney in both sexes were remedied 15 days after treatment, suggesting possible reversibility in the mild toxic effects of the extract.

5. Conclusion

Acute toxicity trials indicated a LD50 value of *Momordica foetida* extracts greater

than 5000 mg/kg b.w. dose, suggesting that the leaf methanol extract of the plant is non-toxic and could be safely used in unique dosage administration. However, prolonged oral administration of the methanol extract can lead to mild variation in blood parameters as well as biochemical variations in blood or organs which can be reverted. The methanol leaf extract of *M. foetida* is then a potent candidate for profound pharmacological studies as its use would be safe for the participants.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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